

*Response by Drs. Mathias and Clench:*

We would like to thank Dr. Drossman for his interest and careful review of our papers, "Effect of Leuprolide Acetate in Patients with Moderate to Severe Functional Bowel Disease: Double-Blind, Placebo-Controlled Study" (1) and "Effect of Leuprolide Acetate in Patients with Functional Bowel Disease: Long-Term Follow-Up after Double-Blind, Placebo-Controlled Study" (2). As we stated in the first Discussion, "This study is the *initial* double-blind, placebo-controlled study of the effect of Lupron Depot 3.75 mg on gastrointestinal disease." We appreciate that the results are preliminary, but every journey begins with a first step.

We initially reported the effects of leuprolide acetate (Lupron, 0.5 mg subcutaneously daily) on five subjects with severe disease whom we treated on an open-label basis (3); those patients had excellent results. Six years later, they continue to do well on the drug. The first double-blind study, using a monthly dose (Lupron Depot 3.75 mg) intramuscularly for three months produced similar good results (1). The important aspect of the patients was that all 30 had failed conventional medication and had symptoms that were disabling. None of the subjects had mild disease. Although the minimum entrance score was 15, the mean baseline scores of the two groups of subjects were much higher—34 and 40 (out of a maximum of 60). In the follow-up study (2), we showed in detail (Table 2) the improvement in patient symptoms according to their individual evaluations. We could have expressed this change in numbers, but numbers alone do not reflect the real outcome.

In the initial phase of the study, we demonstrated that reductions in symptom severity showed progressive improvement with length of treatment; symptom improvement *did not* occur with the placebo group. Thus the study was continued for another year to show full potential efficacy.

The difference in the baseline numbers used in our two reports resulted from our coauthor, P.H. Hsu, PhD, a professional statistician, using the median in the first study to show the change in the Lupron-treated group versus no change in the placebo-treated group. In the follow-up study, the statistical analyses were done by authors who, for reasons of simplicity, used mean values. The outcome, however, was the same. We disagree with Dr. Drossman when he states that there were no significant differences at the end of treatment between active drug and placebo. The leuprolide group began with a mean symptom score of 40 that steadily and progressively dropped to 21.5 after

three months, whereas the placebo group was unchanged—from 34 to 31. We also note that in a randomized study, it is not possible to select the composition of two groups so that their baseline scores are even; none of our groups' clinical characteristics were significantly different (Table 1), and when the baseline scores in a randomized, blinded study turn out to be different (40 vs 34), change from baseline is a more valid comparison to make, not the difference between final scores (21.5 vs 31).

We also appreciate that, although the symptom scores improved significantly in the Lupron group, the between-group differences were not significant in the double-blind, placebo-controlled phase. This may be explained by the small sample, the short therapy period, and the low dose of medication. We are now continuing our clinical investigation of leuprolide acetate and have expanded it to a phase II, multicenter, double-blind, placebo-controlled study, with the number of patients based on a power-exponential determination. This second phase includes three arms: placebo, Lupron Depot 3.75 mg, and Lupron Depot 7.5 mg. Duodenal-jejunal manometry is being performed before and at the end of four months of double-blind therapy. Bowel function is also being assessed in a rigorous manner, and psychological testing and quality-of-life assessment have been added. The effect of the drug on bone density is being determined by bone densitometry. The double-blind, placebo-controlled phase has been increased to four months, with an open one-year follow-up treatment period. We anticipate that this detailed second study will help provide important answers to the use of this drug and solidify our findings in the first study.

Gonadotropin-releasing hormone (GnRH) analogs are not like any other medication currently available for treatment of disease. As we continue to learn more about these analogs' mechanisms of action, it is increasingly apparent that they do not just affect the gonadal hormones, but are powerful modulators of autonomic neural function (4, 5). One of the naturally occurring forms of GnRH (cGnRH II) has been identified in most vertebrate forms, ranging from primitive fish to mammals. In a recent review, King and Millar stated "It is now apparent that GnRH has functions in addition to that of regulating pituitary hormone release, and that the basic structure of the molecule has been recruited during evolution to serve extrapituitary functions" (4). This recruitment appears to be neural. L.E. Muske has postulated that cGnRH II probably evolved with pheromones in nerve cells and only later further evolved as a control